- A1250-1
10/6/87

OCTOBER 5, 1987

CHEMICAL & ENGINEERING

International conference focuses on heteronuclear clusters
Page 31

NEWS

05111179C098 9 K AR654OSL
CONGRESSIONAL INFO SERV-SRI 1
4520 EAST WEST HWY SUITE 800
SRI ACQUISITIONS
BETHESDA MD 20814

ANIMAL DRUGS

Strong growth is resuming **Page 51**

CHEMICAL & ENGINEERING NEWS

Volume 65, Number 39
CENEAR 65 (39) 1–108
ISSN 0009-2347

OCTOBER 5, 1987

News of the Week

■ **Catalytic role of chlorine in depletion of stratospheric ozone over Antarctica is confirmed, according to preliminary data from Antarctica expedition.** **Page 6**

■ **In effort to boost role of minorities in science and engineering, National Science Foundation establishes first two centers under its new Minority Research Centers of Excellence program.** **Page 7**

■ **Office of Technology Assessment review supports Centers for Disease Control study that said it would not be possible to identify which Vietnam veterans were exposed to agent orange.** **Page 7**

■ **Conservationists urge overhaul of U.S. environmental policies and institutions to deal effectively with environmental problems.** **Page 8**

■ **NL Industries halts attempts to spin-off its chemical unit, more than a year after it first announced its plan to spin-off the unit.** **Page 8**

Cover: Veterinarian injects banamine antiarthritic agent at Schering-Plough's animal health research center, Cream Ridge, N.J. Photo copyright John Alexanders, Black Star

Letters 4

Concentrates

Business 11
Government 19
Science/Technology 26

The Departments

New Products 73
ACS Comment 85
Meetings 87
Newscripts 108

Business

Edwin Holmer, this year's Society of Chemical Industry medalist, takes a retrospective look at the petrochemicals industry. **Page 16**

Government

As preshipment inspections of U.S. exports increase, chemical firms complain of delivery delays, interference with negotiated prices. **Page 20**

Science

Cluster chemistry opens new vistas in organometallic research, leads to commercial breakthroughs in catalysis, ceramics. **Page 31**

Attendees of workshop on scientific fraud and misconduct offer different professional perspectives on this complex issue. **Page 44**

Books

Author Maurice Goldsmith advocates need for "science critic" to help enhance understanding needed to form public policy. **Page 74**

ACS News

National Chemistry Day plans advance, in what promises to be most publicly visible program ever for the society. **Page 80**

Product Report

Growth in animal health products market resumes, in response to return to profitability of livestock industry, increased research spending, and changes in government regulatory climate. **Page 51**

Chemical & Engineering News

1155—16th St., N.W., Washington, D.C. 20036
Editor: Michael Heylin
Assistant Managing Editors: David M. Kiefer, James H. Krieger, Janice R. Long, Donald J. Soisson, William J. Storck
Staff Editor: Ernest L. Carpenter
Senior Editors: New York: Earl V. Anderson; Chicago: Joseph Haggin; Washington: Lois R. Ember, Wilbert C. Lepkowski, Rebecca L. Rawls
Associate Editors: Stuart A. Borman, Mairin B. Brennan, Doron Dagani, Bette Hileman, Richard J. Seltzer, Pamela S. Zurer
Service Departments Editor: Dolores Miner
Editing Services: Joyce A. Richards (Head), Anne Riesberg (Editorial Assistant), Patricia Oates (Administrative Assistant)

News Bureaus: New York: (212) 697-3223 Stephen C. Stinson (Associate Editor), Marc S. Reisch (Assistant Editor). Chicago: (312) 256-4143 Ward Worthy (Head). Houston: (713) 973-8161 Bruce F. Greek (Head). Washington: (202) 872-4495 David J. Hanson (Associate Editor). West Coast: (415) 653-3630 Rudy M. Baum (Head). **Foreign Bureau:** London: (01) 540-0414 Dermot A. O'Sullivan (Head), Patricia L. Layman (Associate Editor)
Graphics and Production: Leroy Corcoran (Manager). Alan Kahan (Art Director). Barbara Fryer (Production/Art Director). Linda Mattingly (Staff Artist). Diane Kelly (Costing). **Business Manager:** Arthur Poulos
Circulation Development: Cynthia G. Smith

ADVISORY BOARD: William J. Bailey, Jacqueline K. Barton, Ernest H. Drew, Harry G. Drickamer, A. Nicholas Filippello, Myron Foveaux, Vincent L. Gregory Jr., Adam Heller, John D. Holmfeld, Donald F. Hornig, Isabella Karle, Dorothy Nelkin, Richard Nicholson, Howard A. Schneiderman, Ellen K. Silbergeld, Howard E. Simmons, William P. Slichter, Richard N. Zare

Published by
AMERICAN CHEMICAL SOCIETY
(202) 872-4600; TDD (202) 872-8733
John K Crum, Executive Director

PUBLISHING BOARD: Barbara G. Wood (*Chairman*); *Board of Directors Chairman:* Ernest L. Eliel; *President:* Mary L. Good; E. E. McSweeney; John H. Nelson; Louis D. Quin; and Jean'ne M. Shreeve
© Copyright 1987, American Chemical Society

Subscription Service: Send all new and renewal subscriptions with payments to: Director, Business Management Division, ACS, P.O. Box 57136, Washington, D.C. 20037. Correspondence and telephone calls for changes of address, claims for missing issues, subscription service, status of records and accounts should be directed to: Manager, Membership & Subscription Services, ACS, P.O. Box 3337, Columbus, Ohio 43210; (614) 421-3776.

For changes of address, include both old and new addresses with ZIP code numbers and mailing label from a recent issue. Allow four weeks for change to become effective. Claims for missing numbers will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated (a) North America: more than 90 days beyond issue date, (b) all other foreign: more than one year beyond issue date; or if the reason given is "missing from files."

Subscription Rates 1987. Printed editions: nonmembers U.S. 1 yr. $44, 2 yr. $75, outside U.S. 1 yr. $70, 2 yr. $127. Air freight rates available on request. Rates above do not apply to nonmember subscribers in Japan, who must enter subscription orders with Maruzen Co. Ltd., 3-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103, Japan. Tel: (03) 272-7211. Single copies: Current $6.00. Rates for back issues and volumes are available from Microforms & Back Issues Office, ACS, 1155—16th St., N.W., Washington, D.C. 20036. Back and current issues available on microfilm and microfiche. Rates on request from Microform Program, ACS.

Chemical & Engineering News (ISSN 0009-2347) is published weekly except for the last week in December by the American Chemical Society at 1155—16th St., N.W., Washington, D.C. 20036. Second-class postage paid at Washington, D.C., and additional mailing offices. POSTMASTER: Send address changes to Chemical & Engineering News, Membership & Subscription Services, P.O. Box 3337, Columbus, Ohio 43210. ACS assumes no responsibility for the statements and opinions advanced by the contributors to its publications.

Advertising Management
CENTCOM LTD.
(For list of offices see page 107)

LETTERS

Safe hotplates

SIR: The report of the explosion during peroxide treatment of fiber samples (C&EN, Aug. 3, page 2) raises appropriate points not only about nomenclature, but also about ceramic-topped hotplates.

A few years ago, a pedologist in our earth science department borrowed the use of my perchloric fumehood to treat clay samples with perchloric acid according to a well-established procedure. The samples, in beakers, were moistened with diluted perchloric acid and heated in a sandbath on a Corning ceramic-topped hotplate. Before the work was abandoned, three hotplates had been shattered. Fortunately, no pieces flew more than a few inches, but still-live heating elements were exposed.

The point to remember seems to be that for some purposes, metal-topped hotplates are much to be preferred for safety.

G. F. Atkinson
Associate Professor of Chemistry
University of Waterloo, Ontario, Canada

Nuclear waste disposal

SIR: I am responding to a comment made by George W. Price (C&EN, July 27, page 3). According to Price, the solution to nuclear waste disposal problems is to set aside a square mile of desert, build a warehouse, and surround it with a cyclone fence posted with signs saying, "If you cross this fence you will die." I happen to live in the desert Southwest, and I like it here. One man's wasteland is another man's paradise. If Price wishes to build a nuclear waste dump, let him volunteer a square mile of midwestern lake shore (maybe somewhere in the Chicago area) and keep his hands off my desert.

Mike Hosea
Las Cruces, N.M.

Fraud and coauthorship

SIR: Inaccuracies in a recent letter by Ravi K. Agrawal (C&EN, Aug. 10, page 4) detract from his comments regarding fraud and coauthorship.

A more careful reading of the News Focus article "Misconduct in Research" by Pamela S. Zurer (C&EN, April 13, page 10) would have provided the information that when a postdoctoral research associate of Alex Nickon submitted fabricated research results for publication, he did so totally on his own. Referral to the original literature in question confirms that Nickon is not a coauthor of the fraudulent papers themselves, nor is he cited in the subsequent refutations of these papers. The study might have provided additional perspective for Agrawal's examination of the principles, practices, and responsibilities of coauthorship in the chemical sciences.

Martin Hulce
University of Maryland Baltimore County
Catonsville

Doing business with China

SIR: It seems to me that the article on U.S.-China trade (C&EN, Aug. 10, page 6) omits an important factor that contributes to limiting the success of U.S. companies doing business with China. As someone who spent several years before retiring in seeking opportunities in China for my last employer, I had ample opportunity to observe the efforts of many companies from around the world in that country. My conclusion is that non-U.S. companies have entered that arena with a plan/strategy and a commitment to stay in there for the long haul whereas their U.S. counterparts take a more opportunistic approach.

The article correctly touches on the difficulties of dealing with the "intricate Chinese bureaucracy" and this will not change for some time. However, companies wishing to establish a position of any kind there must take into account limitations such as the bureaucracy, scarce hard currency, etc. that exist now, and establish a position for the future.

T. L. Heying
Consultant
Clearwater, Fla.

Antibacterial peptides

SIR: I write after reading the science article by Ron Dagani, "Antibacterial Peptides Isolated from Frogs" (C&EN, Aug. 17, page 27). The article is prompted by the publication by M. Zasloff [*Proc. Natl. Acad. Sci.*, **84**, 5449 (1987)] of the amino acid sequence of two 23-residue peptides isolated from the ventral skin of the toad *Xenopus laevis*, and the observation that these peptides (named magainin 1 and magainin 2) possess antimicrobial activity. The characterization and activity of these peptides have been hailed in the *New York Times* (July 31) and the *International Herald Tribune* (July 31) as a great discovery by the National Institutes of Health. Zasloff is cited in

Preshipment Inspection of U.S. Exports Irks Chemical Industry

With inspections increasing, chemical firms complain of delivery delays, higher transaction costs, interference with negotiated prices

David J. Hanson, C&EN Washington

The sweeping trade legislation now being considered by a House-Senate conference committee contains many provisions designed to protect U.S. jobs and open up markets for U.S. exports. These provisions include, in part, an extension of the government's tariff negotiating authority, certain restrictions on trade with nonmarket economies, and mandatory retaliatory actions against nations with excessive trade surpluses with the U.S., if reductions in those surpluses cannot be negotiated.

Although all these are important, another aspect of international trade has been getting considerable attention lately but is virtually untouched in the trade bill. That is the operation within the U.S. of preshipment inspection (PSI) companies, who, working under contract from foreign countries, ensure that U.S. exports to those countries meet quality, quantity, and other requirements. These companies have expanded enormously in the past few years, and, in the opinion of many exporters, have become a considerable nuisance to trade.

They became such a problem, in fact, that last September four trade associations in Florida filed a petition seeking government action against five Caribbean and Latin American nations because the preshipment inspection companies hired by these countries allegedly created a major impediment to U.S. exports. The petition was subsequently withdrawn when the Office of the U.S. Trade Representative (USTR) launched a five-point action plan to investigate the alleged problems.

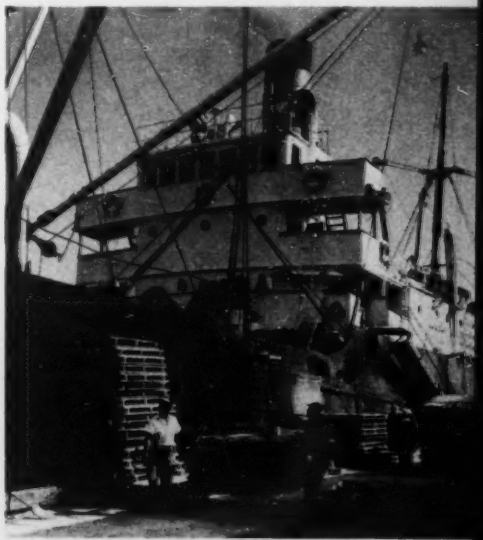
The plan includes monitoring of preshipment company activities and complaints from exporters, and initiation of discussions with a number of nations to try to determine the scope of the problem. The office also has held bilateral discussions with the nations that use preshipment inspection firms to see if the practice can be discouraged. And, as a final resort, the trade representative is looking into legislation that might ease the problem. But the first major step set out in the action plan was a fact-finding study by the International Trade Commission (ITC). That report was released in late August.

Two hearings were held by ITC—one in Florida and the second in Washington, D.C. Testimony from exporters, individuals, and the private inspection companies provided the agency with the information for its report. Particularly striking about the issue is that the chemical industry appears to have more troubles with the inspection companies than any other group. Chemical companies, appropriately, are among the severest critics of these inspection companies.

Current activities of private inspection companies have three especially bothersome results, according to exporting companies. First, the inspections delay the delivery of goods, a critical factor for pharmaceuticals that might deteriorate in quality because of the delay, and for chemical commodities that have to arrive on time to meet process requirements. Second, an inspection results in increased documentation and transaction costs for the exporter. Third, there is widespread concern that the inspection companies arbitrarily interfere with negotiated prices.

Although the problems alleged by the exporters have mostly come about in the past three years, preshipment inspections have been conducted for many years. According to the ITC report, ever since the 1800s individual exporters and companies have used independent inspections to verify the quality and quantity of commodities moving in international trade. Companies still use it today. This provides some guarantee that the proper amounts and quality of products are maintained during the shipping process. The fees for independent inspection services are paid for by either the purchaser or supplier.

In the late 1960s, some African countries, responding to enormous debts and flight of scarce foreign capital, contracted with private com-



Preshipment inspections of exports have risen markedly in past few years

panies to help them prevent fraud in their imports and exports. Their emphasis was still on verifying the quality and quantity of shipments.

The current controversy arose when nations in the Caribbean and Latin America began hiring PSI companies to help them control capital flight by getting a handle on imports. However, a new twist was added to the traditional inspections. In addition to quality and quantity verification, the PSI firms now were also verifying the prices of shipments to ensure that the exporter was not overcharging the importing nation. It is price verification that has become one of the more contentious problems.

"Quite simply, preshipment companies can and do unjustifiably interfere with negotiated price agreements between an exporter and an importer by employing inspection standards that vary from the objective formula and statistically acceptable practices used to establish market prices," said Armin F. Vaihinger, marketing manager for the international department of the Geon Vinyl division of B. F. Goodrich to ITC in April. "The chemical and pharmaceutical industries are where there has been an intrusion from a price point of view, because the inspection companies just don't know how to get a handle on the prices," says Max Turnipseed, manager of international trade affairs for Ethyl Corp. In trying to find an acceptable market price for a commodity, "they are trying to get into something that it has taken years for people in the industry to understand," he says.

The ITC investigation determined that PSI firms use a variety of yardsticks to measure prices. These include market information from commercial sources, publications of trade associations, government reports, the manufacturer's price list, or comparable current sales invoices from other shipments. ITC concludes, however, that there appears to be no specific formula used in performing price comparisons.

For their part, the inspection companies say they are doing what their contracts call for and are providing a useful service. In the U.S. there are three preshipment inspection companies working for foreign nations. The largest by far is SGS Control Services, which is a subsidiary of Société Générale de Surveillance, headquartered in Geneva. In 1986, 23 of the 25 nations that require preshipment inspection employed SGS, according to ITC. Other PSI operations in the U.S. are performed by Intertek Services International of Fairfax, Va., which works with the British company Caleb Brett International. The third firm is the French company Bureau Veritas.

PSI companies claim that several advantages arise from the use of their services. The foremost is that, by protecting a nation from excessive capital flight, PSI promotes economic growth and new market opportunities for U.S. exporters in those developing nations. According to Franklin D. Kramer, attorney for SGS Control Services in Washington, D.C., "It is critical to recognize that the countries put these programs on a worldwide basis because of the problems they face at home." Inspections also are supposed to streamline import and customs procedures in developing countries and encourage responsible behavior by exporters of all nations, to the advantage of U.S. companies that must comply with the Foreign Corrupt Practices Act. During the ITC investigation, SGS backed up these claims with letters from U.S. banks and investment institutions praising the PSI company's efforts to meet these goals.

Exporters, however, don't see the situation quite the same way. Ralph Chew, president of the National Federation of Export Associations, told ITC commissioners, "To a large extent, PSI activities are a phony program to pretend that the problem of capital flight is being solved. The direct and indirect costs of PSI activities are simply out of proportion to any benefit derived from them." Ida Watson, manager of foreign regulations and export services for Hercules, agrees that PSI companies are a problem. "Inspection

U.S. chemical exports to countries using preshipment inspection have declined in past two years

$ Thousands	1986	1985	1984	1983	1982
Angola	$ 2,452	$ 4,424	$ 2,981	$ 2,562	$ 4,293
Bolivia	4,364	6,374	7,576	8,712	7,791
Burundi	0	37	33	1	3
Congo	610	362	90	201	578
Ecuador	125,433	119,774	105,168	80,745	117,657
Equatorial Guinea	0	0	0	3	124
Ghana	19,892	4,548	1,637	6,895	37,303
Guatemala	76,089	75,921	83,321	78,528	81,627
Guinea	368	3,304	570	734	806
Haiti	13,022	14,402	15,449	14,409	14,662
Indonesia	216,422	167,271	238,201	252,942	251,169
Ivory Coast	9,548	5,363	5,550	8,035	9,223
Jamaica	45,693	48,288	51,846	53,382	73,608
Kenya	11,827	15,862	10,310	16,832	10,115
Liberia	2,694	3,545	3,576	4,807	4,212
Madagascar	1,035	1,436	697	522	73
Mexico	1,255,669	1,408,560	1,268,664	1,104,564	1,187,955
Nigeria	42,890	54,161	44,269	52,204	52,578
Paraguay	4,520	4,507	3,310	3,277	9,430
Rwanda	18	12	115	5	27
Surinam	15,059	22,363	26,222	29,481	29,084
Tanzania	7,563	4,394	13,337	2,424	3,971
Uganda	41	121	402	68	310
Venezuela	491,428	448,596	553,527	376,524	493,204
Zaire	2,261	3,155	2,671	3,037	3,465
Zambia	731	4,141	6,122	3,061	7,210
TOTAL	$2,349,629	$2,418,921	$2,445,644	$2,103,955	$2,400,478

Source: U.S. Department of Commerce

Another item for your

LANTHOLOGY

*of Ln's * in modern chemistry*

These ten

LANTHANIDE METALS

now available

as ingots or chips

ERBIUM
DYSPROSIUM
TERBIUM
GADOLINIUM
SAMARIUM
PRASEODYMIUM

NEODYMIUM
CERIUM
LANTHANUM
YTTRIUM

...and alloys thereof

Booming interest in the separated lanthanide metals for these uses...

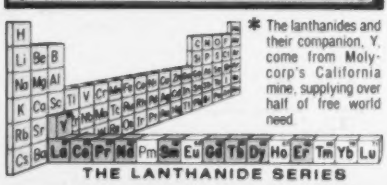
- **Permanent magnets (Dy,Nd,Sm,Pr)**
- **Erasible optical disks (Tb,Gd,Dy)**
- **Hydrogen-storage alloys (La)**
- **Aluminum alloys for higher temperature service (Ce)**
- **Magnetostrictive devices (Tb,Dy)**
- **Heat-resistant MCrAlY metals (Y)**
- **Dispersion-strengthened nickel and titanium alloys (Y,Er)**
- **Oxidation-resistant aerospace engine parts (La,Ce)**
- **Improved Mg castings (Y,Nd), and**
- **Superconductor precursors (La,Y)**

...is demanding quantity production with control over purity.

Molycorp has geared up to meet that demand. Write for specification sheets; phone for technology support. 1553

UNOCAL 76
MOLYCORP

MOLYCORP, INC. • A Unocal Company
709 Westchester Ave., White Plains, NY 10604
Tel. 914/997-8880 • TWX 710/568-0305



* The lanthanides and their companion, Y, come from Molycorp's California mine, supplying over half of free world need.

THE LANTHANIDE SERIES

CIRCLE 71 ON READER SERVICE CARD

companies have been known to arbitrarily reject our prices," Watson says, "even after documentation has been given to support the price. We view these PSI activities as an unfavorable restraint of trade." This was echoed by Anthony Barone of Warner-Lambert speaking on behalf of the Pharmaceutical Manufacturers Association. "Given current massive trade deficits, U.S. companies need to export. But the activities of the PSI companies are dissuading U.S. companies from selling their products abroad," he says.

Trade is being hampered, exporting companies say, because of the direct and indirect costs of inspections. Although the PSI company's fees are paid for by the importing country (between 1 and 2% of the shipment price, according to the ITC investigation) there is a cost to the exporter. Much of this comes from increased paperwork and shipping delays. "It roughly takes two weeks longer, plus or minus a day or two, for us to have papers ready for presentation of payment on a shipment that is subject to PSI as compared with one that is not subject to inspection," says Ethyl's Turnipseed. "Even when there are no questions being raised about the price, no hitches of any kind, just the sheer paperwork is a built-in delay," he says. This has been denied by the PSI companies.

During the ITC investigation, many companies reported problems in getting inspectors to the shipments when needed. Even SGS admitted that some of the delay was due to the very large increase in the number of countries using PSI firms and a lag in these companies' ability to keep up. ITC reported that the shipping process took 14 days longer, on average, for shipment to countries that require PSI than to those that do not. Of 178 chemical companies responding to an ITC survey, 35 cited costly delays as their primary concern with PSI.

Speaking for SGS, attorney Kramer says that this situation has been largely corrected. One step SGS has taken since the complaints were filed is the opening of a new center in Miami, which handles all of the SGS South American programs in the U.S. Kramer goes on to say that

C&EN staff photo

Turnipseed: sheer paperwork is delay

greater internal use of computers and communications of exporters with PSI companies by electronic mail have helped speed the process. "We also have instituted an appeals process," Kramer says, "so a person with a problem can appeal directly to our president and have that problem looked at promptly."

Yet, at least for the chemical industry, the problems persist. "It's fine to say that all the problems are over, but that's just not the case," says K. James O'Connor, the legislative representative for international trade at the Chemical Manufacturers Association. "There has been some improvement in some situations only because SGS has targeted some of the more vocal critics." Turnipseed agrees. "At Ethyl, we still experience the same level of delay, whether the price is questioned or not," he says. "There is a built-in delay of at least five working days before you can get the paperwork processed." And these delays are costing exporters and manufacturers money.

The ITC report concludes that the average cost to an exporter from delays caused by PSI is about $530 per shipment, although CMA's O'Connor estimates that the value is closer to $750 for chemical companies. Much of this cost results from extra personnel hired to follow through with the procedure. Added to that are the extra courier

fees and telephone calls associated with PSIs and monetary losses due to delayed payments. "Your money is tied up somewhere from producing a good," O'Connnor says, "and you're paying interest on that money until it's paid back. So PSI, which is delaying shipment for up to three times as long as when PSI is not required, is costing you."

Another serious concern of the chemical industry is the requirement that they give the PSI company confidential business information before the inspection company will allow payment on a shipment. ITC says that chemical exporters have complained loudly that information such as prices to individual customers, contractual arrangements, product formulas, and data on price calculation are being demanded by inspection firms. This information is often considered proprietary, especially in the competitive chemicals and pharmaceuticals markets, by companies and by the federal government. Many instances have been recorded of PSI firms telling a manufacturer the price of a competitor's product while doing a price inspection. Also, paperwork has been delivered to the wrong company, revealing competitors' prices.

SGS says that the information it requires is not confidential business information, but is information that is available to many other persons and organizations such as customs services, banks, exporters, and insurance companies. Attorney Kramer says that SGS has even revised its "request for information" form "to make it clear we are only asking for a limited amount of information so exporters do not feel they have to turn over the whole store."

There is also the problem that PSI companies offer no guarantee that they will try to maintain the confidentiality of the information they collect. ITC reports that some firms have been able to make informal arrangements for confidentiality on a case-by-case basis, but at least one case is recorded where a chemical company asked SGS to sign a secrecy agreement covering company data and SGS refused. Turnipseed says that no one is sure what the PSI companies do with the data they collect, but in SGS's case there is

Experience the Genzyme World of Fine Chemicals

At Genzyme Fine Chemicals our comprehensive custom chemical services can provide a wide range of products to meet your specifications. Backed by 25 years of experience, we can scale-up from laboratory synthesis and continue through to bulk scale production.

For further information on Genzyme Fine Chemicals, call Toll-Free (in the U.S.) **1-800-332-1042.**

Products available in bulk include:

- Chiral Intermediates
- Fluorobenzenes
- Fluoronitrobenzenes
- Fluoroanilines
- Bromobenzenes
- Bromoanilines

Custom Synthesis also available. Contact Genzyme today.

genzyme fine chemicals

In the U.S.
Carolyn Bellerose
Genzyme Corporation
75 Kneeland Street
Boston, MA 02111
In Mass. (617) 451-1923
TELEX (U.S. 25) 201223
FAX (617) 451-2454

In the U.K. or Europe
David Hopkins
Genzyme Fine Chemicals
37 Hollands Road
Haverhill, Suffolk CB9 8PU
(0440) 703522
TELEX 81333 GENFIN
FAX (0440) 707783

CIRCLE 38 ON READER SERVICE CARD

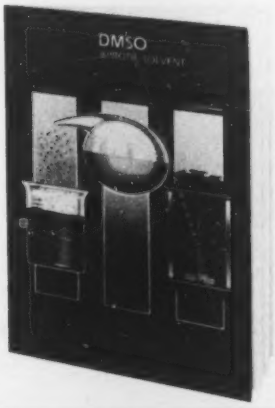
LOOKING FOR A POWERFUL SOLVENT, A COST EFFICIENT REACTION MEDIUM, OR AN EFFECTIVE REAGENT?

YOU'VE FOUND ONE.

DMSO (dimethyl sulfoxide) has a unique combination of high polarity, thermal stability, low toxicity and easy handling that make it ideal for a wide variety of industrial applications.

Including, possibly, yours. Send for our free brochure to find out more.

ATOCHEM INC. elf aquitaine group ATO



Send me a copy of your booklet on DMSO.

Name_____

Title_____

Company_____

Address_____

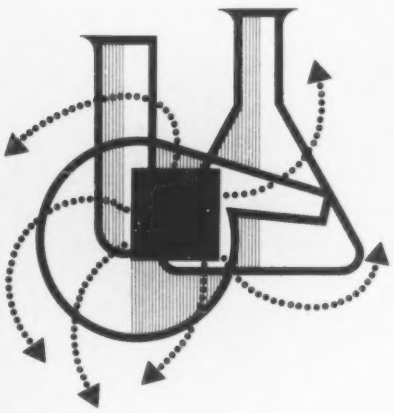
City_____ State_____ Zip_____

Phone_____

ATOCHEM INC
P.O. Box 607
Glen Rock, NJ 07452
U.S.A.
Phone
1-800-932-0420
(In NJ 201-652-8575)

ATOCHEM
Direction Chimie Fine
et de Specialites
Cedex 42
92091 Paris--La Defense
FRANCE
Phone (1)49 00 80 80
Telex ATO 611922 F

CIRCLE 9 ON READER SERVICE CARD



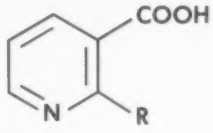
HEXACHIMIE

a highly qualified team and specialized knowledge in

FINE CHEMICALS

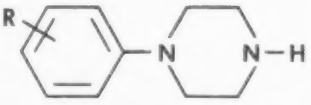
FOR THE PHARMACEUTICAL INDUSTRY

• **The 2-position of nicotinic acid**



R = Cl, NH-Ar,...

• **Arylpiperazines**



R = Cl, F, OH, OCH_3, OC_2H_5, CH_3, CF_3,...

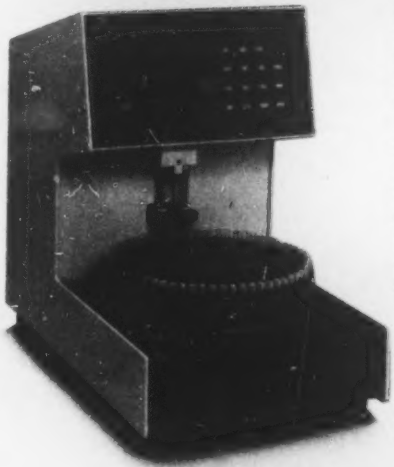
Hexachimie s.a.

Head and commercial offices:
128, rue Danton - 92504 Rueil-Malmaison - France
Phone: (1) 47.49.05.00 - Telex: 203 269

R & D unit, production and control:
47240 Bon-Encontre - France - Telex 550 842

CIRCLE 42 ON READER SERVICE CARD

New HPLC Autosampler



Highest reliability and precision

- RS-232-C standard
- Requires no auxiliary gas
- Works with any HPLC system
- Interfaces with any valve

Micromeritics' new Model 728 Autosampler uses a patented positive displacement sampling technique to eliminate the need for an auxiliary gas supply. It provides the highest reliability and precision on the market at the lowest cost, using state-of-the-art microcomputer technology.

micromeritics

One Micromeritics Drive, Norcross, GA 30093-1877
Telephone (404) 662-3669 FAX (404) 662-3696

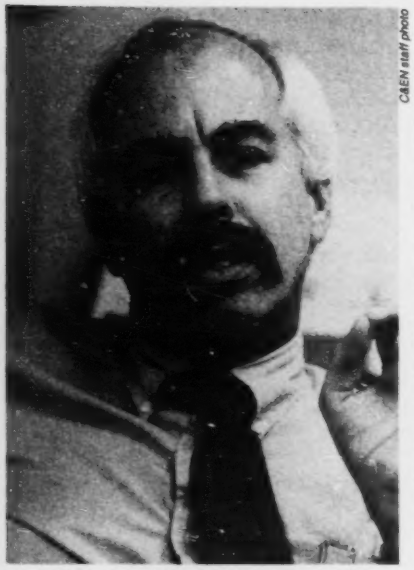
CIRCLE 80 ON READER SERVICE CARD

evidence that they are sent on to the home office in Geneva. If so, there is some concern that the data could be used by Swiss-based international trading or banking firms competing against U.S. interests.

To top off all the mechanical and nuisance problems U.S. exporters are having with PSI companies, they have serious doubts that the nations hiring the companies are getting their money's worth. "Factually, there is no way to be certain," says Turnipseed. He claims that some countries are obviously not pleased with the service they are getting. Jamaica, which has had a PSI agreement for only a year, has dropped its contract with SGS. Guatemala and Ecuador are reconsidering their present contracts and may not renew them. Bolivia is also changing its PSI contract. Peru is the latest major South American country to begin a new PSI program, and its continuance will be contingent on the inspection company proving that it is saving the country at least twice the program's cost.

There is evidence in the ITC study that appears to back up the claim that countries may not be saving as much as they had hoped. All the PSI firms operating in the U.S. were found to question prices more often than product quality, ITC reports. Yet savings from price reductions amounted to only 1.2% of the total value of shipments reported inspected by the three companies. Companies answering the ITC survey reported that a total of $1.8 million in revenues were lost because of forced price reductions in 1986. This may not be enough to recover the expenses a nation has had in hiring the PSI company in the first place. The inspection companies claim there have been significant savings resulting from deterrence of price gouging, but this cannot be documented. Industry representatives, not unexpectedly, say there has never been a problem with fraud by U.S. exporters, and there is no need for price inspections.

And price inspections aren't the only area where companies have doubts. The quality and quantity inspections are not what they should be either. "With regard to Ethyl, not once have [the inspection com-



C&EN staff photo

O'Connor: PSI can be very costly

panies] inspected any of our shipments for quality." says Turnipseed. "They have never taken a sample. Not once. And only on less than 10% of shipments have they ever questioned quantity." He says that the company has laboratory analyses done on all bulk shipments, whether a PSI is going to be done or not, and PSI companies have just taken that private report and accepted it. Chemical and pharmaceutical companies question whether PSI inspectors are qualified to make quality determinations without sending samples to a lab. John Saunders, manager of international programs for the New York Chamber of Commerce & Industry, told ITC, "Many inspectors lack the product knowledge necessary to perform their tasks, and, as a result, many of the inspections are no more than cursory appraisals of highly sophisticated products."

In addition, exporters claim that the nations hiring PSI companies are violating terms of the General Agreement on Tariffs & Trade, especially Article VII on the customs valuation code, which, in part, prohibits the use of arbitrary or fictitious customs values. SGS counsel Kramer says the position of his company is that the nations employing inspection companies are not signers of the tariff agreement and are not bound to its stipulations.

Even so, PSI companies argue that their actions are consistent with the valuation rules, maintaining that the article in question allows importing countries to compare prices for like merchandise as they are determined "in the ordinary course of trade." The chemical industry has testified otherwise. It told ITC that the PSI programs go beyond what is reasonable even if the objectives are legitimate. "PSI programs . . . amount to totally unreasonable and unacceptable government practices regulating—no, disrupting—international trade," Turnipseed says.

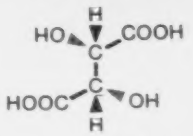
If agreements cannot be reached among the parties involved, Congressional action may result. Some European countries, where PSI problems are also on the increase, have passed laws limiting the activities of PSI companies. In the U.S., a last-minute amendment to the House trade bill by Rep. Daniel A. Mica (D.-Fla.) to regulate PSI companies has been criticized by all sides and probably will be dropped when the bill is in conference committee. Donna LaTorre, acting director of the Congressional Export Task Force, says that PSIs are not a big concern at the moment, but there is a move to hold hearings on the issue in the Senate next year that could lead to new legislation.

Industry thinks there could be another way around the problem. If foreign nations feel that mandatory PSI inspections are necessary for U.S. exports, then the place to do them is in the importing country, Turnipseed says. The inspection companies could do their job at the importing end and probably save the nation money, he contends. Exporters, if there was a concern, could put up a bond to assure the shipment was proper, an action commonly done already.

The problem may not seem like a major issue in the scope of all international trade, but it is a real one. Although not a major economic burden to major companies, small exporters and manufacturers can be hurt badly. "It's a specious argument to say that PSI doesn't cost that much," says CMA's O'Connor. "If you're the product manager of a company that is being hit with price reductions and delays, it's costing you a lot." □

'TORAY'

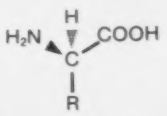
D(-)-Tartaric Acid



CIRCLE 74 [CAS No. 147-71-7]

- Large quantity (ton lot) available.
- Attractive price to use.
- Derivatives ((+)-dibezoyl-, (+)-di-p-toluoyl-, (−)-diesters-) also available.

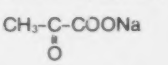
D-Amino Acids



CIRCLE 75

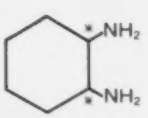
D-Alanine	[CAS No. 338-69-2]
D-Glutamic Acid	[CAS No. 6893-26-1]
D-Aspartic Acid	[CAS No. 1783-96-6]
D-Serine	[CAS No. 312-84-5]

Sodium Pyruvate



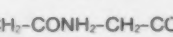
CIRCLE 76 [CAS No. 113-24-6]

trans-1,2-Diamino-cyclohexane



CIRCLE 77 (R,R)-[CAS No. 20439-47-8] (S,S)-[CAS No. 21436-03-3]

Glycylglycine



CIRCLE 78 [CAS No. 556-50-3]

TORAY INDUSTRIES (AMERICA), INC.
280 Park Avenue, New York, NY. 10017, U.S.A.
Tel:1-212-697-8150 H.Morimoto/K.Koshiishi
Telex:233067 (TAMI UR).

TORAY EUROPE, LTD.
7th Floor, 35/38 Portman Square, London, W1H0BS, England
K.Nishikawa/J. McNeille
Tel:44-1-4869374~6
Telex:919176 (TORAY G)

TORAY INDUSTRIES (JAPAN), INC.
Specialty Chemicals, Dept.
2-2-1, Nihonbashi-Muromachi, Chuo-ku, Tokyo 103, JAPAN
Tel:(03)245-5692, 5616
Telex:J22623 (TORAYINC)

CIRCLE 74-78 ON READER SERVICE CARD

Hoechst-Roussel Agri-Vet Co.

Animal Health Products Recovering Momentum

Steven C. Stinson, C&EN New York

The U.S. market for animal health products climbed 6% in 1986 from 1985 to $2.1 billion, according to the Animal Health Institute (AHI), which represents producers of animal health products. AHI ascribed the rise to the return to profitability of the livestock industry. Business Trend Analysts, Commack, N.Y., predicts that this trend will continue, leading to annual growth rates of 5% over the next 10 years.

During the high-inflation period from 1977 through 1980, animal health products grew 15% yearly in current dollars. From then through 1986, subsiding inflation coupled with a depressed farm economy limited annual growth to 2%.

The Commack consulting firm also cites changes in the government regulatory climate and increased research spending by industry as factors that will contribute to renewed growth. The one-time concern over use of subtherapeutic levels of antibiotics in feed has abated, leading to resumption of prosperity in that product area. Development of safer, more effective drugs is a further spur to increased dollar sales. And the weakened dollar is tending to strengthen exports as a source of sales to U.S. producers.

The relatively exposed living conditions of animals, whether outdoors or housed, the manner of feeding them, and the economics of keeping them all make the marketing climate for animal health products strikingly different from that for human drugs. Of the $844 million spent in 1986 for veterinary drugs, for example, AHI says that $233 million went for antimicrobials and $611 million for such products as hormones, antiseptics, drugs against internal and external parasites, and vitamin and mineral supplements.

Animal owners purchased $193 million worth of biologicals in 1986. This category includes vaccines, tox-

Thirty-five major firms supply U.S. animal health market

A. L. Laboratories
Affiliated Laboratories
Agri-Bio Corp., subsidiary of A. H. Robins
Agripharm division of Osborne
American Cyanamid
Anchor
Beecham
Bio-Ceutic
Bristol-Myers
Ceva
Cutter division of Miles
Elanco division of Eli Lilly
Fort Dodge Laboratories
Gentocinge Laboratories
Haver
Hess & Clark
Hoechst-Roussel Agri-Vet
Hoffmann-La Roche
MSD Agvet division of Merck
Norden
Pfizer agricultural division
Pitman-Moore, subsidiary of IMC
Rhône-Poulenc
Roche
SDS Biotech
Salsbury
Schering Animal Health
SmithKline
Solvay Veterinary
Sterwin Laboratories
Syntex
TUCO division of Upjohn
TechAmerica
Tri-Mutual
Whitmoyer

Source: Business Trend Analysts

oids, immune sera, and blood and blood products.

The $1.07 billion market for feed additives is the largest component of the animal health market. This is because antibacterials ($269 million), vitamins and minerals ($548 million), and antiparasiticals are added to feed also.

Managers in the animal health industry and veterinarians classify the animals in different ways. Some speak of domestic (farm), companion (pet), and zoo (exotic species) animals. Others use the terms large (farm animals), poultry, and small (dogs, cats, and caged birds). Many think of horses as companion animals when compiling statistics.

The economics of medicating animals changes with each class. Owners of domestic animals constantly compare costs of treatment to results obtained. Business Trend Analysts does point out that use of animal health products increases livestock production 4 to 32% and saves owners $3.00 for every $1.00 spent.

By contrast, owners of companion animals tend to spare no expense in treating their pets. Zoo veterinarians have the same attitude toward individuals in their collections. Zoo budgets are tight, though, and veterinarians there often rely in part on donations of money and products from companies.

The distribution of animal health care products also differs from that of human drugs. For instance, there are over-the-counter (OTC) drugs and drugs restricted to veterinary use only ("restricted drugs"). At first sight, these correspond roughly to human OTC and prescription drugs. But the Food & Drug Administration allows professional animal owners freer access to drugs as OTC products than to laypersons treating themselves. The criterion for OTC classification is whether the drug producer can write instructions that animal owners can understand and follow easily.

Thus farmers can buy oral and injectable antibiotics and antiparasiticals at farm supply stores. But these same drugs are classified restricted for companion animal veterinary practice.

Farm animals also get antibiotics and antiparasitical drugs in their feed. Medicated feed is produced by about 12,000 companies in the U.S. Among the largest are Ralston-Purina, Carnation, Congra, and Land O'Lakes. These companies sell in turn to 13,000 of the 19,000 farm supply stores in this country.

The picture is complicated by the fact that many large farms have feed mills capable of blending batches of a few tons. These farmers buy antibiotics and antiparasiticals directly and blend them into their feed. Many of these farmers form farmer-dealer organizations and sell the medicated feed to their neighbors.

Likewise the U.S. poultry industry has become so concentrated that a few large producers such as Perdue buy drugs directly from pharmaceutical companies for production of medicated feed.

Dispensing of restricted veterinary drugs also differs from that for human prescription drugs. There are virtually no veterinary pharmacies where animal owners can take prescriptions to be filled. Thus veterinarians usually dispense the restricted drugs they recommend.

Many veterinarians resent the efforts of drug companies to get OTC classification for their products. These practitioners feel that these efforts undercut their roles in recommending and dispensing drugs. For their part, drug company managers feel that they must market OTC as well as restricted brands of drugs to maximize sales.

Other veterinarians have begun stocking their own inventories of OTC drugs. This move has stirred criticism from some practitioners that there is a conflict of interest in both recommending and selling OTC products. Some drug company observers feel that this criticism is justified. They point out that many veterinarians are little skilled in maintaining adequate inventories and estimating suitable markups. These observers say that veterinarians' true role is professional advice. Other drug company observers say that the move to dispense OTC drugs is a logical extension of veterinary practice, and that more veterinarians should join this obvious trend.

It is difficult to estimate the relative amounts spent on drugs for farm animals versus those for dogs, cats, and horses. AHI does not break its data out completely in this way. The American Veterinary Medical Association (AVMA) does compile information about the relative amounts spent for total veterinary care, only part of which is for drugs.

AVMA estimates that Americans spent a total of almost $5 billion for veterinary services in 1985, the latest year for which data are available. Of this, $3 billion was for dogs,

$1.1 billion for cats, $210 million for horses, and about $640 million for dairy and beef cattle, swine, and sheep combined. Thus dogs, cats, and horses accounted for 87% of the total.

The number of cats in the U.S. (50 million) outstripped the number of dogs (49 million) for the first time in 1985, according to the Pet Food Institute. Although the number of cats continued to grow strongly to 56.2 million in 1986, compared with 51.6 million dogs, this trend may not translate into strong growth in veterinary drug sales. This is because AVMA estimates that only half of cat owners take their pets to veterinarians, whereas three quarters of dog owners do so.

Discovering and developing new animal health products is the task of some three dozen companies in the U.S. Of these, the largest is Pfizer, whose agricultural division will sell about $520 million worth of veterinary drugs this year. Division president Roland M. Hendrickson says that half its sales are for feed additives and half for pharmaceuticals.

Hendrickson says that Pfizer has more new veterinary drugs in development than at any time in its history. The cycle of product introductions that these will fuel will propel the company's growth for the next 10 years, he says. Among these, three are especially promising.

Ionophores are often used to treat coccidiosis in poultry

One is a quinolone antibacterial that is expected to counter the resistance of serious animal pathogens. Pfizer is developing an injectable form for cattle and swine and a water-soluble powder to be added to poultry drinking water. The second Hendrickson describes as a novel drug effective against a wide range of internal and external parasites. The third is an ionophore that is very promising against coccidiosis, a protozoan infestation of the intestine that causes greatest problems in poultry but occurs also in cattle, sheep, and swine. At present, the most popular drugs against coccidiosis are the ionophores monensin from Eli Lilly and salinomycin from A. H. Robins.

For the more distant future, Pfizer is working on genetic engineering projects, notably on a vaccine against heartworm in dogs, liposomes for enhanced drug delivery, and agents to improve digestibility of animal feed.

Hoechst-Roussel Agri-Vet Co.

Swine eat feed containing fenbendazole, which rids them of worms

Biotechnology projects are important at many companies besides Pfizer, and they are bringing the philosophy of veterinary medicine full circle. As veterinary medicine emerged from the symptomatic treatment and quackery of the 19th century, veterinarians pinned their hopes on vaccines and antitoxins for treatment and prevention of disease. This is because they despaired of finding chemotherapeutic agents.

Then in 1932, pathologist Gerhard Domagk at Bayer's laboratory for experimental pathology and bacteriology in Wuppertal-Elberfeld, West Germany, discovered that Prontosil 4-(2,4-diaminophenylazo) benzenesulfonamide cured otherwise lethal bacterial infections in mice. Others later found that this compound was metabolized to sulfanilamide. This discovery of the first sulfa drug had greatest impact

Dog owners benefit from breakthrough in treating heartworm

Approval of Merck's ivermectin by the Food & Drug Administration in 1986 for heartworm in dogs was a boon to their owners.

This oral drug need be given only once a month during the mosquito season to prevent infection. Mosquitoes transmit infective larvae. Veterinarians previously advised giving oral diethylcarbamazine citrate daily without skipping a single day.

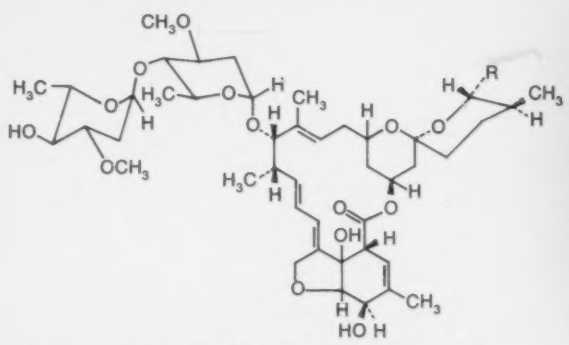
Once confined to the mid-Atlantic, South, and Gulf coasts and Mississippi River valley, this parasite has become endemic in dogs east of the Rocky Mountains in the past 20 years. Only 20% of dogs are dosed with preventive drugs, which leaves the rest as potential reservoirs for spread of heartworm.

Parasitologists distinguish several life forms of heartworm (*Dirofilaria immitis*), but there are three important ones—infectious larvae, adult worms, and microfilariae. Mosquitoes deposit infective larvae on dogs' skin. The larvae penetrate through breaks and migrate through tissues and the bloodstream to the heart and pulmonary vessels, maturing to adults in 60 days.

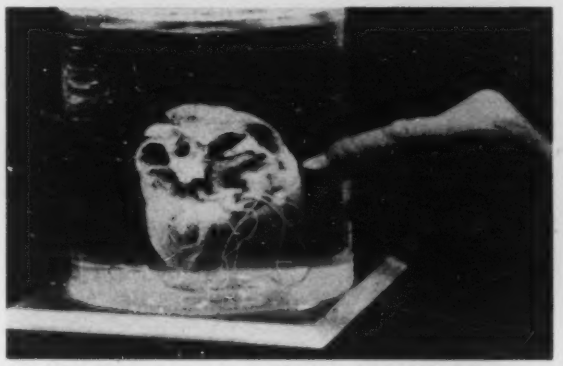
Adults grow to 9 to 14 inches in length, clog the heart and its blood vessels, and can cause congestive heart failure in dogs. Adult worms reproduce sexually to spawn microfilariae, which circulate in the blood. When they bite infected dogs, mosquitoes ingest microfilariae, which evolve into infective larvae in the flies' kidney tissue.

Ivermectin kills infective larvae but not adult worms or microfilariae. Because infective larvae take 60 days to mature to adulthood, the next dose can be given in 30 days to kill any that have entered between doses.

Veterinarians can begin treatment of infected dogs with thiacetarsamide to kill adult worms, followed by dithiazanine to kill microfilariae. They can start ivermectin therapy at once in uninfected dogs and in others after ridding them of adult worms and microfilariae. Puppies may be treated with ivermectin at six weeks old.



Ivermectin contains more than 80% of 22, 23-dihydroavermectin B_{1a} (R = *sec*-butyl) and less than 20% of 22, 23-dihydroavermectin B_{1b} (R = isopropyl)



Adult heartworms live in canine heart and pulmonary arteries, reducing or blocking blood flow

on human medicine, but the philosophical implications were not lost on veterinarians. They could develop chemotherapeutic agents to supplement their biological ones.

Now, 50 years later, the rapidly developing techniques of biotechnology are being recruited by veterinarians to invent vaccines and antibodies against disease organisms. And whereas biologicals of the past were directed against bacteria and viruses, the newest work also focuses on more advanced parasitic organisms.

Pfizer's discovery of new agents occurs at the firm's research center in Groton, Conn., with developmental testing at the company's farm near Terre Haute, Ind. The veterinary research group at Groton is separate from the human medicinal units there, although they share support services. Hendrickson estimates that bringing new agents from discovery to FDA approval costs $50 million each. This amount includes money spent on compounds that must later be abandoned.

Yet he points out that the animal health market is only one tenth the dollar value of the human one. A product that eventually reaches $30 million in yearly sales is a big success for a veterinary drug, though puny for a human one. Thus Pfizer must develop worldwide marketing to support its ambitious research program.

One factor Hendrickson cites as increasing costs of biotechnological products is efforts to counter objections of outside critics. Though loyal to Pfizer, Hendrickson praises American Cyanamid's work on bovine somatotropin to raise milk production. Critics question the value of adding to dairy products already in oversupply. But as Hendrickson puts it, "It's ridiculous to talk of ignoring anything that improves efficiency."

Veterinary medicinal research is more narrowly focused at Schering Animal Health, a division of Schering-Plough Corp. Division president Karl Meister says he concentrates on unique, patented, potentially high-volume agents for both food and companion animals that can be marketed on a worldwide basis.

"You must keep in mind that animal health is not a growth market," he says. "So to be a superior competitor, you must do your own research for unique patented products, and develop a critical mass." Schering Animal Health works on veterinary drugs and biologicals but

INTERMEDIATES FOR PHARMACEUTICALS

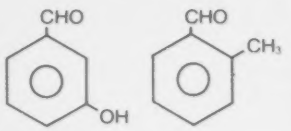
=BIOCHEMICALS=

Adenine
Guanine
Deoxy-D-ribose

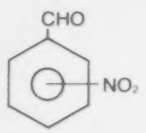
=D-AMINO ACIDS etc.=

D-Alanine
D-Glutamine
D-Tartaric acid

=AROMATIC ALDEHYDES=

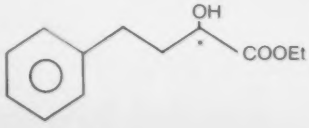


=NITRO ALDEHYDES=



o.m.p–NBA

2(R)-Hydroxy-4-phenyl BAE



NAGASE & CO., LTD.

TOKYO
NAGASE & CO., LTD.
Chemical 2nd Div.
5-1, Kobunacho, Nihonbashi
Chuo-ku, Tokyo, Japan
Tel. 03-665-3370 (Mr. Miura)
Telex. J26480

NEW YORK
NAGASE America Corp.
500 5th Ave. New York
N.Y. 10110, U.S.A.
Tel. 212 354-3140 (Mr. Nishimura)

DUSSELDORF
NAGASE (Europa) GmbH
Am Wehrhahn 41
4000 Düsseldolf 1
F.R. Germany
Telex. 8588686 (Mr. Yamashita)

CIRCLE 52 ON READER SERVICE CARD

avoids generic compounds and feed additives. The division pursues products that can be approved in both restricted and OTC forms as part of their search for that marketing critical mass.

Some of the division's new products grow out of human medicinal chemistry at Schering's central research facilities. The division licenses such new nonhuman drugs as antihelminthics and coccidiostats from other companies. Veterinary pharmaceuticals are tested in development at the company's farm in Cream Ridge, N.J., and biologicals at its farm in Elkhorn, Neb.

Among biologicals, Schering Animal Health is very active in vaccines. Meister is particularly proud of a recent one for Potomac horse fever, a bacterial disease that kills up to 50% of its victims. The division is also seeking vaccines against equine rhinopneumonitis and influenza, heartworm, and coccidiosis. Schering Animal Health has done its own biotechnological work toward some of these products to date but is also seeking agreements with smaller biotechnology firms.

The research philosophy at Merck's MSD Agvet division starts as far back as how farmers can produce more food with fewer, more efficient animals, says William H. D. Leaning, executive director of technical services, which follows performance of agents after approval and feeds back suggestions for new dosage forms, uses, or product types.

So far this has led the division into what Leaning calls applied parasitology. For example, some cattlemen minimize the importance of parasite control, even though parasites impair weight gain in young animals. The rationale is that parasite control is costly, animals usually overcome infestations themselves, and there is a compensatory weight gain later.

But MSD Agvet has done work to show that this later weight gain is mostly fat. Moreover, parasites generally slow the growth of medium- to fast-growing muscle tissues, which turn out to be the more prized and expensive cuts of meat. So divisional representatives try to persuade farmers that parasite control ultimately repays them with more efficient meat production.

In addition, heifers reach breeding weight sooner with parasite control. This results in a longer, more productive breeding life. And dairy farmers can increase milk production, allowing them to achieve quotas with fewer cows.

The concentration on applied parasitology has led MSD Agvet to depend on a few products in comparison with other firms, but two of these have been blockbusters. First, Merck developed the antihelminthic

Growth resumes for animal health care products

	Sales, $ millions					
Type	1986	1985	1984	1983	1982	1981
Pharmaceuticals	**$ 844.0**	**$789.6**	**$ 764.0**	**$ 759.1**	**$ 684.0**	**$ 597.7**
Antimicrobials	232.9	220.9	214.7	214.8	204.8	197.2
Other	611.1	568.7	549.3	544.3	479.2	400.5
Biologicals	**192.9**	**192.0**	**167.6**	**171.5**	**148.7**	**152.6**
Large, food-producing animals	69.3	73.1	72.8	76.6	70.4	89.4
Poultry	40.3	37.4	33.5	33.3	23.0	23.6
Small animals	55.4	55.1	34.4	37.4	47.7	59.6
Rabies	10.2	9.8	10.9	9.5	a	a
Equine	17.7	16.6	16.0	14.7	12.9	a
Food additives	**1066.8**	**999.6**	**1046.9**	**1097.9**	**1081.1**	**1078.3**
Antibacterial	269.1	270.6	283.1	268.6	248.2	239.5
Nutritional	547.7	498.4	540.0	597.7	613.9	632.1
Other	250.0	230.6	223.8	231.6	219.0	206.7
TOTAL	**$2103.7**	**$1981.2**	**$1978.5**	**$2028.5**	**$1913.8**	**$1828.6**

a Included in figure for small animals, then called companion animals. **Source:** Animal Health Institute

thiabendazole 25 years ago, which revolutionized treatment then and still sells well today. The most recent agent is ivermectin, which is effective against a wide spectrum of both internal and external parasites. The company also developed clorsulon against liver flukes and amprolium against coccidiosis.

Ivermectin is effective for long periods at vanishingly small oral or injected doses against not only a variety of tissue and gastrointestinal nematodes (round worm-types), but also such external parasitical and disease-carrying insects and arachnids as fly larvae, lice, mites, and ticks. The dose in cattle and horses is about 200 μg per kg of body weight, and that for heartworm in dogs is 6 μg per kg. As with thiabendazole earlier, MSD Agvet is pursuing approvals in most countries of the world for various dose forms, species in which to be used, and parasites to be controlled.

Ivermectin acts in parasites by stimulating release of the neurotransmitter γ-aminobutyric acid (GABA) from nerve cells. This overloads the nervous system, causing paralysis and death. Mammals have GABA-mediated nerve transmission only in the central nervous system, and ivermectin does not cross the blood-brain barrier.

In other product areas, MSD Agvet tried to get into vaccines several years ago. But Leaning explains that vaccines themselves cannot be patented, and other, small producers were duplicating these products. These others could market their vaccines without FDA approval as long as they did not deal out of their own states. But microorganisms that produce vaccines can be patented. So the division's future plans include inventions of new vaccines by genetic engineering for a return to the market.

And the company's overall philosophy of improving efficiency of food production is leading it into such areas as partitioning agents. These are synthetic amphetamine-like drugs that accelerate fat metabolism and slow turnover of muscle fiber. Such agents might increase efficiency of meat production in cattle and poultry.

The research effort at Hoechst-Roussel Agri-Vet Co. concentrates on food-producing animals. Research on new compounds is conducted by Hoechst in Frankfurt and by Roussel-Uclaf near Paris. Recently developed products include fenbendazole, which group product manager Terry Sheehan cites as an improvement in effectiveness over thiabendazole as an anthelminthic. The company also received FDA approval for halifugenone for coccidiosis in 1985. Sheehan says this drug is more potent and less costly to use than ionophores now on the market. And coccidia do not develop resistance against it as they have against other nonionophore agents.

Approval was given this year for trenbolone acetate, an anabolic steroid that improves feed use efficiency in cattle and increases the ratio of muscle to fat. For the future, the company is seeking approval for altrenogest, which suppresses heat in mares and sows. When the drug is withdrawn, animals come quickly into heat so that stockmen can plan breeding times.

Pig farmers can use it to develop herds whose ages are about the same. Horse owners can use it to breed mares at optimum times. Racing rules state that a horse becomes officially one year old on Jan. 1 of the year after it is born. Thus a horse born in December 1986 must already race as a two-year-old after Jan. 1, 1988.

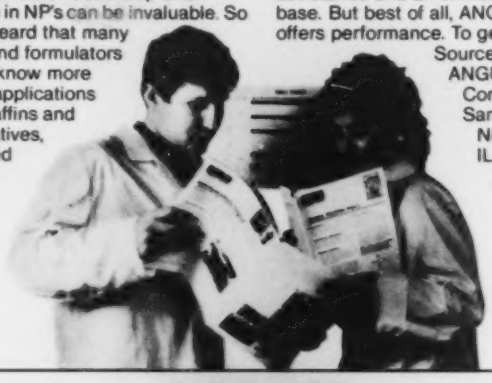
For the veterinary pharmaceutical industry as a whole, Rainer K. Muser sees several problem areas that still need solutions. Muser, who is director of R&D at Hoechst-Roussel Agri-Vet Co., sees liver flukes as a continuing scourge. Though drugs are available to kill them, these agents are often effective against only one of the life forms. Existing drugs kill adults in animals' bile ducts. Drugs under development kill larval forms. Muser sees a vaccine as a possible, ultimate treatment.

ANGUS PERFORMS™

We heard you when you asked for more data on the uses of nitroparaffins and their derivatives.

If you seek new products or improved products, ANGUS' leadership and experience in NP's can be invaluable. So when we heard that many chemists and formulators wanted to know more about the applications of nitroparaffins and their derivatives, we prepared a Product Source Guide.

ANGUS also offers sampling, technical assistance and an unmatched data base. But best of all, ANGUS offers performance. To get your New Source Guide, write: ANGUS Chemical Company, 2211 Sanders Road, Northbrook, IL 60062. Or call.



ANGUS®
CHEMICAL COMPANY

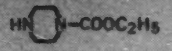
AC-9137

Call 800/323-6209. In Illinois, call collect at 312/498-6700. © 1987 ANGUS Chemical Company

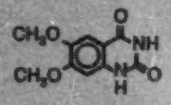
CIRCLE 4 ON READER SERVICE CARD

ORGANIC INTERMEDIATES FROM SWITZERLAND

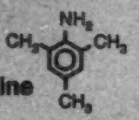
for
- pharmaceuticals
- agrochemicals
- dyestuffs
- flavors
- fragrances
- photochemicals



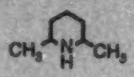
1-Ethoxycarbonylpiperazine



6,7-Dimethoxy-quinazoline-2,4-dione



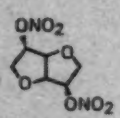
2,4,6-Trimethylaniline
Mesidine



2,6-Dimethylpiperidine, cis

1,3-Cyclohexanedione

Isosorbide dinitrate (ISDN)
mixtures with lactose etc., USP XXI



4-Aminoacetophenone

US-Agents:
HENLEY CHEMICALS, INC.
50, Chestnut Ridge Road
Montvale, NJ 07645
Phone (201) 307-0422

SSF DOTTIKON

CH-5605 Dottikon/Switzerland
Phone (057) 26 11 55
Telex 827 923 ssf ch

CIRCLE 67 ON READER SERVICE CARD

Vitamin E: How much is enough?

Veterinary physician Emil P. Dolensek is fond of pointing out that studies in zoos can be more revealing than those with laboratory animals. This is because zoo populations contain many species, are genetically diverse within species, and range from newborn to aged animals.

Dolensek, who heads the Animal Health Center at the New York Zoological Society (the Bronx Zoo), recently used the worldwide resources of the society to detect hitherto unsuspected pathologies of vitamin E deficiency. His findings may affect how stockmen manage farm animals.

The trail began in 1983, when Dolensek noted that five Mongolian wild horses at the zoo that lacked coordination in their hind quarters had been destroyed in the previous five years because of their condition, and one afflicted animal had died foaling. Pathologists found areas of destruction of myelin sheaths and nerve cells in the animals' spinal cords at the lower cervical and upper thoracic vertebrae.

Blood chemistries and urinalyses were normal except for abnormally low serum levels of vitamin E. All animals had been fed hay, green grass in summer, and commercial horse pellets supplemented with vitamin E.

One problem was that the optimum levels of vitamin E in exotic species was unknown. Dolensek turned to Wildlife Conservation International, a research branch of the society with scientists in 30 countries. These sent him blood samples of elephants, hippos, black rhinos, and dugongs in the wild, which were compared with samples from the same species at the zoo. Vitamin E levels in captive animals were found to be much lower than those in the wild.

Dolensek's work was hampered at first by lack of money. But Perkin-Elmer Corp. donated a liquid chromatograph for high-volume determinations of vitamin E. Technicon gave an Autoanalyzer for analyses of cholesterol and lipids, which are related to vitamin E. And Hoffmann-La Roche, a vitamin E producer, granted money to pay the salary of a nutritionist from Cornell University to work at the zoo.

In further search of pathology from vitamin E deficiency, Dolensek correlated the medical and maintenance records of animals that had died unexpectedly over the previous 10 years with the "library" of tissues preserved from them. At the zoo, all animals that die of any cause are examined postmortem and tissue samples preserved.

He zeroed in on about 100 animals of the deer family, eight baboons, and about 100 embryos and chicks of six bird species that had failed to hatch or died within days of hatching. The hearts of all of these showed destruction of muscle and replacement by fat or fibrous tissue. In animals whose serum vitamin E levels were determined at the time, these were abnormally low. The feed of all of them and the chicks' and embryos' hens had been supplemented with vitamin E.

Dolensek concluded that levels of vitamin E supplementation were too low. Curators increased the vitamin E content of animal feeds sharply. Heart disease in mammals and birds has not been seen at the zoo since 1983.

Dolensek notes that vitamin E is also important in reproduction. This fact may affect owner practices in feeding farm animals as well.

Again, drugs are available to prevent coccidiosis but must be given constantly in poultry feed, which is expensive. Again, the solution may be a vaccine.

There is also a need for antibiotics against bacterial diseases that will treat them economically. With the withdrawal of FDA approval of chloramphenicol for use in food animals, Muser says that there is a lack of a good antibiotic for such gram-negative bacteria as salmonella.

A common problem Muser cites in the cattle industry is bovine pneumonic pasteurellosis. Because this can strike all and especially young cattle during shipping to market, it is called shipping fever. The disease, which takes many forms, is a bacterial pneumonia caused by Pasteurella, combined with and brought on by stress, exposure, poor

Chemists worldwide rely on Resoflex R-296

the only truly compatible resinous, non-volatile, non-migrating plasticizer for polyvinyl acetate.

RESOFLEX R-296

Cambridge Industries Co.

440 Arsenal St.
Watertown, Mass. 02172

Custom-made resinous products for industry since 1946

CIRCLE 84 ON READER SERVICE CARD

How drugs get their generic names

Carbadox. Fenbendazole. Ivermectin. Hundreds of new veterinary and human drug candidates get generic names every year. Whatever brand names their sellers eventually give these compounds, the Food & Drug Administration and scientists publishing in journals will use their generic names. And when they go off patent, generic drug companies will probably use their generic names to market them.

American generic names are the etymological brainstorms of the U.S. Adopted Names (USAN) Council, founded privately in 1962 by the American Medical Association, American Pharmaceutical Association (APhA), and U.S. Pharmacopeial Convention to bring order and simplicity to drug names.

The USAN Council has offices at AMA headquarters in Chicago, where Donald O. Schiffman is secretary. Five council members—chemists, pharmacologists, and physicians—who are not paid for their work, are scattered around the country and hammer out new generic names by mail. AMA, APhA, and USP Convention trustees approve a new council yearly. Members may succeed themselves for a maximum of 10 years.

The naming process begins when a drug company asks the USAN Council to name a new compound. The council never refuses a request, Schiffman says, but usually expects the company to go as far as human or target animal testing before asking. Until 1985, naming was free. But staff support and computer search time became too burdensome to AMA, and the council started charging $1000 for new names and $500 for salts or esters of compounds already named.

Over the years, the council has established such stems as -cillin for penicillins, -oxacin for quinolones, and cef- for cephalosporins. This last one has become "a bit of a disaster," Schiffman says. Cef- has the advantage of putting all cephalosporins together in alphabetical listings but makes the growing number of names look alike. Sometimes the council has to live with mistakes.

In the beginning, names came from salient parts of molecular structures. Recently, councilors have favored names that reflect pharmacological action, and they usually name antibiotics from the microorganisms that produce them. They avoid th, which is unpronounceable in some languages, and initial h, which is silent in others. Lack of a y in many alphabets leads to replacement by i.

The council seeks agreement on new names with the drug firms that ask for them, with FDA, and with the International Nonproprietary Names (INN) Committee of the World Health Organization. Schiffman is a member of the INN Committee, which represents nomenclature authorities of individual countries. Trial names are published in the Pharmaceutical Manufacturers Association Bulletin for criticism by its member firms.

Intense drug research in other countries often leads to compounds' getting their first generic names from the INN Committee. In these cases, the USAN Council tries to adopt the INN Committee name, unless insurmountable problems compel the council to create its own.

The council publishes final new names monthly in the *Journal of Clinical Pharmacology & Therapeutics*. The USP Convention publishes an annual dictionary of generic drug names, together with an appendix giving INN names that are different.

nutrition, and viral infection in transit. The present treatment is routine injection of all cattle with penicillin on arrival. There are yet no reliable vaccines against Pasteurella.

There is also no reliable cure for anaplasmosis, a rickettsial blood infection of cattle, Muser says. And atrophic rhinitis is a problem in swine. The latter is an infection of the turbinate bones, a maze of thin plates in the snout, often caused by Pasteurella or Klebsiella. In severe cases the snout is severely deformed, breathing is inhibited, and animals become susceptible to other diseases. There is still no reliable vaccine for this, Muser says, and the present treatment with daily sulfonamides

Lasix commonly used in race horses

Attendees at race tracks in several states may see postings that one or more horses in a race have been given Lasix, an oral diuretic for treatment of high blood pressure in humans.

But most veterinarians believe that injectable Lasix, which is marketed by Hoechst-Roussel Agri-Vet Co., Somerville, N.J., also prevents exercise-induced pulmonary hemorrhage (EIPH). And many veterinarians and trainers believe that regardless of effect on EIPH, Lasix somehow improves racing performance.

Writers have noted for at least 300 years that a few horses finish a race with blood flowing from their nostrils. Racing records of the past 75 years show that up to 6% show this phenomenon, with the average at about 1%.

By the mid-1970s many veterinarians were critical of the practice of administering Lasix to up to 50% of horses at some tracks. These horses' veterinarians and trainers claimed that the horses bled internally, even if blood didn't reach their nostrils.

Then in 1978, veterinary medical professor John R. Pascoe of the University of California, Davis, used the then-new flexible fiber optic endoscope to screen a total of 235 horses within two hours of their racing at one track. Of these, 103 (43.8%) had blood in their tracheas, and two of the 103 later bled from the nostrils.

The cause of EIPH is still unknown. Some veterinarians suggest that tremendous increases in breathing during racing increase pulmonary blood pressures, leading to rupture of small blood vessels in air sacs. Others implicate some form of small-airway disease. With the cause unknown, use of Lasix, steroids, and other drugs that have been tried has been empirical rather than scientific.

Both sexes and all breeds are equally afflicted. EIPH seems more prevalent in horses older than five years than in those younger, and in those that run more than eight furlongs than in those that run fewer. Of horses with a history of EIPH, about 30% will not show it after any one race.

Veterinary medical professors Lawrence R. Soma and Corinne R. Sweeney of the University of Pennsylvania have studied Lasix and EIPH. Horses that suffered EIPH in one race were divided into Lasix-treated and -untreated groups and examined after second races of equal lengths and conditions within 30 days of the first.

Among 85 such horses, a larger percentage of the untreated ones developed EIPH after their second races than Lasix-treated ones. But effects of racing and betting regulations and of trainers' own decisions whether to participate skewed the numbers in each group, and statistical analysis showed no meaningful difference.

Soma also has studied effects of Lasix on racing times in seconds per km of a total of 128 horses. Horses ran five races on various days without Lasix followed by five races with it. Soma divided them into groups according to whether or when they bled from the nostrils or into the trachea only. He compared these groups with one another and with a group of randomly chosen horses without Lasix. He also compared those that were worth more than $10,000 (better historical performers) with those worth less. Again, there was no meaningful difference.

or tetracyclines in the feed is expensive and not always effective.

Animal populations in zoos pose their own special problems, according to Lyndsay G. Phillips Jr., associate veterinarian at the National Zoological Park in Washington, D.C. For one thing, there are almost no drugs approved for animals there. It is too costly for companies to do all the testing that would be required for FDA approval species by species. So zoo veterinarians are left to extrapolate from treatment of domestic and companion animals of similar species.

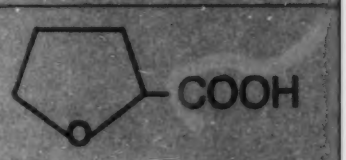
Some antibiotics do not act the same in the "big cats" as they do in house cats, for example. Tigers do not absorb oral tetracyclines as well as house cats. Although half-lives of tetracyclines are the same in both animals, blood levels never reach therapeutic concentrations in tigers.

AVAILABLE FROM QO CHEMICALS

COMMERCIAL PRODUCTS

DEVELOPMENTAL PRODUCTS

3-Furoic Acid



2-Tetrahydrofuroic Acid

For more information, write or call:

QO Chemicals, Inc.
Subsidiary of Great Lakes Chemical Corp.
823 Commerce Drive
Oak Brook, Illinois 60521
Phone: 312-572-2308

QO CHEMICALS

QO-1123

CIRCLE 14 ON READER SERVICE CARD

New drug, altrenogest, would allow mares to be bred at optimum times

And reptiles are even more susceptible than humans and other mammals to the kidney-damaging side effects of aminoglycosides. At the National Zoo, veterinarians have worked out a regimen of giving gentamicin to reptiles at 72-hour intervals.

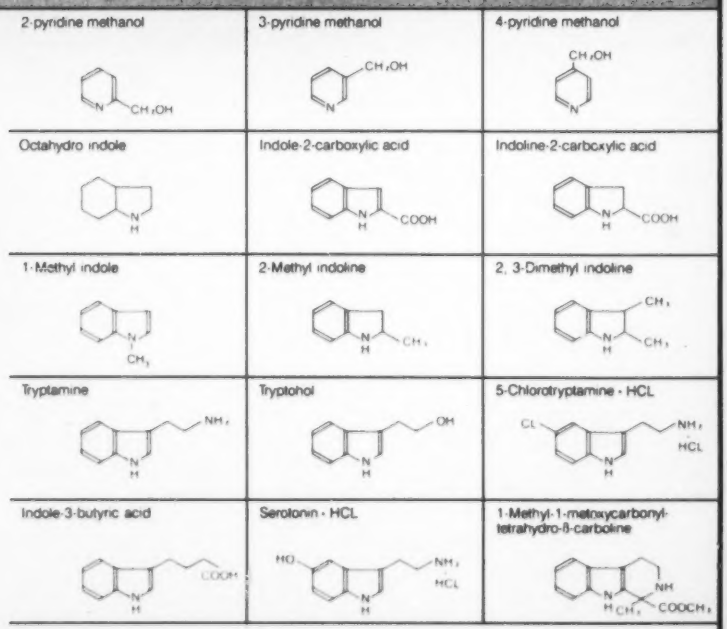
On a positive note, there do not seem to be as many antibiotic-resistant strains of bacteria in zoos, Phillips says. They find that most cases of bacterial infection are susceptible to the six to 10 antibiotics they routinely screen for. Antibiotics most used are ampicillin, carbenacillin, erythromycin, oxytetracycline, gentamicin, kanamicin, and some cephalosporins. There is a preference for long-acting penicillins to avoid the stress of dosing an animal more than once daily.

Another challenge in zoo practice is anesthesia. Animals respond differently, depending on species, sex, size, health status, and age, Phillips says. But the staff has gained a lot of experience with anesthetic doses. Recovery is also variable. Some animals awaken delirious.

"You can watch four hours of surgery destroyed in a few minutes," Phillips says. "We're very protective of the animals. We keep them in the dark away from stimuli so they just sleep it off. We keep them in crates or stalls, and we watch them to see that they don't get a head or a foot caught." □

For the Best in Pyridine, Indole, and Quinoline Derivatives, You Can Rely on Kawaken

That's because we are a world leader in the production of these and a wide range of other chemicals used in the pharmaceutical and agrochemical industries.



For more information write:

KAWAKEN Fine Chemicals Co., Ltd. 6-6, Kobuna-cho, Nihonbashi, Chuo-ku, Tokyo 103, Japan
TELEX 252-2326 FINETK J TELEPHONE (03)663-9521

CIRCLE 45 ON READER SERVICE CARD